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New guidelines to treat bacterial infections

The release of the new guidelines to treat infections caused by drug-resistant Gram-negative bacteria by IDSA is most welcome. Ammara Mushtaq and Farooq Kazi report.


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On Sept 8, 2020, the Infectious Diseases Society of America released new guidelines for treating infections caused by three types of drug-resistant Gram-negative organisms: 1) extended spectrum β-lactamase producing Enterobacterales (ESBL-E) 2) carbapenem-resistant Enterobacterales (CRE), and 3) difficult-to-treat resistant *Pseudomonas aeruginosa* (DTR-P). The guidelines also describe when newer antibiotics like ceftolozane-tazobactam, ceftazidime-avibactam, imipenem-relebactam, meropenem-vaborbactam, and cefiderocol are appropriate to use.

"5 years ago, clinicians had to use polymyxins, which are toxic and relatively ineffective, to treat most carbapenem-resistant Gram-negative infections because we didn't have other options. Now, we have three new β-lactam/β-lactamase inhibitor antibiotics that target the most common type of carbapenem-resistant enteric bacteria and an additional β-lactam/β-lactamase inhibitor that targets highly-resistant *P aeruginosa*", says Michael Satlin, Weill Cornell Medicine and NewYork-Presbyterian Hospital, New York, USA. "We have new tetracycline derivatives, a siderophore cephalosporin, and a new aminoglycoside that also add to our armamentarium", adds Satlin, referring to eravacycline, cefiderocol, and plazomicin, respectively. However, he cautioned that there are still problematic Gram-negatives for which treatment options are extremely limited—metallo-β-lactamase (MBL) producing enteric bacteria, *P aeruginosa* and *Acinetobacter baumannii*. "We are also seeing increasing resistance to our new β-lactam/β-lactamase inhibitor antibiotics", adds Satlin.

The report separates treatment of cystitis from other sites of infection outside of the urinary bladder, and points to the potential role of non-β-lactams in treatment of the former. For cystitis caused by ESBL-E and CRE, fluoroquinolones, co-trimoxazole (trimethoprim-sulfamethoxazole) and nitrofurantoin are options. For CRE causing cystitis, a single dose of an aminoglycoside is an additional option. For ESBL-E causing infections outside of the urinary tract, however, carbapenems are preferred. Similarly, cefepime should also be avoided for treatment of all infections caused by ESBL-E.

Of note, the combination of ceftazidime-avibactam with aztreonam is now recommended for the treatment of MBL producing organisms. Other options for treatment of MBL producers include cefiderocol and eravacycline (if treating intra-abdominal infection). "Ceftazidime-avibactam largely solves the problem of OXA-48—most isolates are susceptible. MBLs are still a problem. We don't have aztreonam/avibactam yet and have resorted to ceftazidime-avibactam plus aztreonam 'cocktail' a number of times—especially where we have strains with both NDM-1 and OXA-48", says David Wareham, Queen Mary University of London, UK.

For DTR-P, ceftolozane-tazobactam, ceftazidime-avibactam, imipenem-relebactam, cefiderocol, or aminoglycosides are recommended treatment options. Combination therapy is not routinely recommended for infections caused by DTR-P. If the listed newer agents do not have activity against *P aeruginosa*, then aminoglycoside (if susceptible) can be given in combination with either ceftolozane-tazobactam, ceftazidime-avibactam, or imipenem-relebactam, preferentially selecting the drug for which the minimum inhibitory concentration is closest to its susceptibility breakpoint.

These guidelines can be invaluable for international physicians. *Salmonella* Typhi, a common Gram-negative bacterium, has shown an increasing trend towards multidrug-resistant and extensively drug-resistant (XDR) phenotypes. "Between 2016 to 2018, Pakistan saw a large epidemic of XDR typhoid, resistant to all β-lactam antibiotics, and sensitive only to carbapenems and macrolides. This has led to increased empiric use of these antibiotics for presumed infections in the community. With increasing use of meropenem as a result of typhoid, an overall rise in carbapenem resistance in community-acquired infections is inevitable", explains Fyezah Jehan, Aga Khan University, Pakistan.

Lastly, WHO fears that the COVID-19 pandemic may exacerbate antimicrobial resistance. "We are still learning how COVID-19 has impacted antimicrobial resistance. Many critically ill patients remain on a ventilator for weeks to months and thus are at high risk of developing infections caused by multidrug-resistant bacteria" says Satlin. Studies have shown that 72% of patients with COVID-19 received antibiotics while only 8% tested positive for superimposed bacterial or fungal co-infections. Use of biocidal agents for personal disinfection is also concerning. Hence, healthcare providers should use the most up-to-date clinical guidelines for judicious use of antibiotics to avoid an even greater calamity.

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